UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/607,571 | 06/26/2003 | Richard P. Batycky | 2685.2046 US3 | 6287 |

38421 7590 09/21/2009

ELMORE PATENT LAW GROUP, PC
515 Groton Road
Unit 1R
Westford, MA 01886

| EXAMINER | |
|---|---|
| ALSTRUM ACEVEDO, JAMES HENRY | |
| ART UNIT | PAPER NUMBER |
| 1616 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 09/21/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 10/607,571
Filing Date: June 26, 2003
Appellant(s): BATYCKY ET AL.

Ms. Darlene A. Vanstone, Esq.
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed July 28, 2009 appealing from the Office action mailed December 10, 2008.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

Claim 171 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

| | | |
|---|---|---|
| 2005/0074498 | Tarara et al. | 4-2005 |
| 2003/0215512 | Foster et al. | 11-2003 |
| 6,102036 | Slutsky et al. | 8-2000 |

*The Physician's Desk Reference, 56th edition*, **2002**, pg. 1236 (EpiPen® Autoinjector).

Warren et al., "Systemic Absorption of Inhaled Epinephrine," *Clin. Pharmacol. Ther.* **1986**, *vol. 40, No. 6*, pp 673-678.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

(A) Claims 140-143, 153, and 156-160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036).

***Appellant Claims***

Appellants claim a method for administering epinephrine to a patient in need of epinephrine comprising administering spray-dried particles from a dry powder inhaler to the respiratory system of a patient in a single, breath-activated step, the particles comprising (a)

epinephrine or a salt thereof and, (b) at least one pharmaceutically acceptable excipient, wherein the particles administered to the patient comprise at least about 50 micrograms of epinephrine, have a tap density of less than 0.4 g/cm$^3$, and possess a fine particle fraction of less than 5.6 microns of at least about 45 percent.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

Tarara discloses engineered particles that may be used for the delivery of a bioactive agent to the respiratory tract of a patient. The particles may be used in the form of dry powders or in the form of stabilized dispersions comprising a nonaqueous continuous phase. In particularly preferred embodiments the particles may be used in conjunction with an inhalation device such as a dry powder inhaler, metered dose inhaler or a nebulizer (abstract).

Tarara discloses that the disclosed powders may comprise the selected agent or bioactive agent, or agents as the sole structural component of the perforated microstructures. Conversely, the perforated microstructures may comprise one or more components (i.e. structural materials, surfactants, excipients, etc.) in addition to the incorporated agent [0040].

Tarara discloses that his invented preparations provide highly flowable dry powders that can be efficiently aerosolized, uniformly delivered, and penetrate deeply in the lung or nasal passages [0050]. Any bioactive agents that may be formulated in the perforated microstructures are expressly held to be within the scope of pharmaceutical preparations taught by Tarara, including bronchodilators and steroids [0069]. Exemplary medicaments of biologically active

agents suitable for used in Tarara's formulations include bronchodilators, such as adrenaline [0070]. Adrenaline and epinephrine are synonyms for the same compound.

In preferred embodiments, Tarara's compositions are comprised of microstructures formed by spray drying [0075]. The mean aerodynamic diameter of the perforated microstructures is preferably less than about 5 microns, and in particularly preferred embodiments less than 2 microns. These particle distributions will facilitate deep lung deposition of the bioactive agent whether administered using a dry powder inhaler (DPI), metered-dose inhaler (MDI), or nebulizer [0126]. Tarara defines fine particle fraction (FPF) as "the percentage of the total amount of active medicament delivered per actuation from the mouthpiece of a DPI, MDI or nebulizer onto plates 2-7 of an 8 stage Andersen cascade impactor." Tarara's formulations preferably have a fine particle fraction of approximately 20% or more by weight of the perforated microstructures (w/w), even more preferably from about 30 to 70% w/w. In selected embodiments the present invention will preferably comprise a fine particle fraction of greater than about 30%, 40%, 50%, 60%, 70% or 80% by weight [0127].

Tarara states that skilled artisans would appreciate that the perforated microstructures of his invention are useful in DPIs used in inhalation therapies [0131]. Currently, the range of dry powder that can be filled into a unit dose container is from 5 to 15 mg, corresponding to a drug loading ranging from 25 to 500 micrograms per dose (i.e. actuation) and bulk reservoir type DPIs can meter between 200 micrograms to 20 mg of powder per actuation [0132].

Tarara discloses that stabilized dispersions of his invented pharmaceutical formulations are particularly suitable for the pulmonary administration of bioactive agents (e.g. adrenaline),

which may be used for the localized or systemic administration of compounds to any location of the body [0186].

Appellant's attention is drawn to Examples X-XII, wherein Tarara discloses the preparation of various pharmaceutical particles comprising active agents, surfactant, and lactose excipient (Example XI), having a tap density less than 0.1 $g/cm^3$. Surfactants are excipients as well. The Examiner would also like to draw the Appellant's attention to Figure 5 in which Tarara discloses the distribution of an exemplary particulate composition in an Anderson cascade impactor as delivered by a DPI and a MDI. It is well known in the art that the different stages of the Anderson cascade impactor correlate to the delivery of particles to different regions of the pulmonary system, with stages 6-7 corresponding to delivery of particles to the deep lung (i.e. alveolar region of the pulmonary system). See for example, Radhakrishnan (U.S. Patent No. 5,192,528), where the correlation of the different stages of the Anderson cascade impactor with different regions of the pulmonary system is described.

Slutsky teaches a breath activated inhaler, which may contain a single dose of a powdered medicament, which is intended to be inhaled by the patient in a single breath (title; abstract; col. 4, lines 47-49; col. 6, lines 27-62; col. 8, lines 50-55 and 60-62; col. 9, lines 25-30; col. 10, line 48 through col. 13, line 42, especially col. 12, lines 38-59). Slutsky teaches an alternative breath-activated inhaler capable of delivering a large dose of powdered medicament in a single breath (col. 12, lines 38-59).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Tarara lacks the explicit teaching that powdered formulations are delivered in a single breath actuated step. This deficiency is cured by the teachings of Slutsky.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been *prima facie* obvious to a person of ordinary skill at the time of the instant invention to combine the teachings of Tarara and Slutsky, because Tarara teaches powdered pharmaceutical formulations for inhalation administration and Slutsky teaches breath-activated inhalers for the administration of powdered medicaments. It would also have been obvious to combine the teachings of Tarara and Slutsky, because as taught by Slutsky, use of Slutsky's invented inhaler would allow one to deliver a large dose in a single breath. An ordinary skilled artisan would have been motivated to utilize an inhaler capable of delivering a therapeutically effective dose in a single breath, because this would clearly improve patient compliance. Patient compliance would clearly be improved, because one would need fewer administrations to deliver a therapeutically effective dose contained in an inhaler. Regarding the amount of epinephrine delivered, Appellants' claims have no maximum limit on the amount of epinephrine delivered, merely that at least 50 micrograms is delivered. The combination of Tarara's invented compositions with Slutsky's invented inhaler would reasonably be expected to deliver at least 50 micrograms of epinephrine, because one can modify the dosage of epinephrine present in an inhaler to ensure the delivery of a therapeutically effective amount of epinephrine and Slutsky's inhaler permits delivery of an entire dose in a single breath. Therefore, an ordinary skilled artisan would have had a reasonable expectation of success upon combination of the prior

art teachings. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(B) Claims 161-162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above, and further in view of Physicians' Desk Reference (PDR, page 1236) (IDS reference, already of record).

***Appellant Claims***

Appellants claim a method as described above in the instant office action wherein epinephrine is administered to a patient suffering from anaphylaxis, edema, bronchoconstriction, bronchospasm, and/or airway constriction.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and are restated above. The teachings of the PDR were set forth on page 7 of the office action mailed on April 6, 2006 mailed and are restated herein below. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and are restated above.

The 2002 PDR teaches on page 1236 that epinephrine is essential in the treatment of anaphylaxis (1st sentence in the section entitled "Precautions"). It also teaches in the "Clinical Pharmacology" section that epinephrine acts to relieve vasodilation and increased vascular

permeability. It also relaxes the bronchial smooth muscles, which alleviates wheezing and dyspnea. Other conditions alleviated by administration of epinephrine are pruritis, urticaria, and angioedema and it may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Tarara lacks the teaching of a method of treatment wherein epinephrine is administered to treat anaphylaxis, edema, bronchoconstriction, bronchospasm, and airway constriction. This deficiency is cured by the teachings of the PDR.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Tarara/Slutsky and the PDR, because Tarara teaches pharmaceutical preparations wherein the perforated microstructures may comprise adrenaline (i.e. epinephrine) active agent and the PDR describes known treatments which utilize epinephrine to treat anaphylaxis, angioedema, and relax the bronchial smooth muscles. A skilled artisan would have been motivated to combine the prior art references, because the PDR is a well-known medical reference consulted by physicians and other medical professionals to determine which medicaments are appropriate to treat which conditions or disorders. A person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references, because Tarara teaches pharmaceutical compositions comprising

adrenaline and the PDR teaches treatments in which the administration of adrenaline is appropriate, such as in the treatment of anaphylaxis, bronchoconstriction, bronchospasm, etc.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(C) Claims 140-143, 146-150, 159, 160, and 162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 2003/0215512) in view of Tarara et al. (US 2005/0074498) and Slutsky (U.S. Patent No. 6,102,036).

***Appellant Claims***

Appellants claim a method as described above in the instant office action.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and are restated above. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and are restated above. The teachings of Foster were set forth on pages 8-10 of the office action mailed on April 6, 2006 and are restated below.

Foster teaches a composition that comprises a mixture of a pharmaceutically acceptable glassy matrix and at least one pharmacologically active material within the glassy matrix. It may be further mixed with a powdered, pharmaceutically acceptable carrier (abstract).

Foster teaches that the powdered composition will be composed of particles having a mass median diameter (MMD) of about 1-5 microns and a mass median aerodynamic diameter

(MMAD) of about 1-5 microns [0051]. The active materials in the composition are active drug substances preferably used for administration via pulmonary inhalation. The unit dosage typically will be between 0.25 mg and 15 mg of total material in the dry powder, wherein the active will comprise about 0.05% to about 99.0% by weight of the composition [0054]. In the dry state the drug or phase containing the active may be either crystalline or amorphous in form [0055]. Active small molecules for systemic and local lung applications for use in Foster's compositions include steroids and bronchodilators, including adrenaline [0056]. Systemic diseases treatable using Foster's compositions are taught in [0060] and pulmonary diseases, which are suitable targets for treatment include, chronic bronchitis, asthma, ARD, COPD, bronchospasm, and bronchial asthma [0061]. In addition to the glass former, the composition may contain other additives (i.e. excipients) [0064], including non-polar amino acids (e.g. leucine) [0068]. The glass former may be used alone or in combination with additives, which may be crystalline or amorphous [0064]. Suitable glass formers include organic carboxylic salts and the most preferable glass formers include sodium tartrate, lactose, etc. [0071] to [0072]. In Examples 15-16, Foster teaches exemplary formulations comprising a small molecule active (albuterol). The Tables in [0232] and [0234] obviously disclose a FPF in the column with the heading "% particle mass < 5 microns in size."

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Foster lacks the teaching of compositions having a tap density of less than 0.4 g/cm$^3$, which is cured by the teachings of Tarara. Foster lacks the teaching of administration in a single breath-activated step. This deficiency is cured by the teachings of Slutsky.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art at the time of the instant application to combine the teachings of Foster and Tarara/Slutsky, because all inventors teach compositions suitable for inhalation pulmonary administration of active agents. A skilled artisan would have been motivated to combine the teachings of Foster and Tarara, because Tarara's compositions provide teachings of desirable physical characteristics of aerodynamically light particles especially suitable for inhalation administration. An ordinary skilled artisan cognizant of the teachings of Slutsky would be motivated to utilize Slutsky's breath-activated inhaler to improve patient compliance and facilitate delivery of a particulate pharmaceutical formulation in the fewest number of administrations. A skilled artisan would have had a reasonable expectation of success upon combination both Tarara and Foster teach adrenaline-containing (i.e. epinephrine) compositions designed for inhalation pulmonary administration. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(D) Claims 163-170 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above, and further in view of Warren et al. (*Clin. Pharmacol. Ther.*, 1986, *40(6)*, 673-678) (already of record).

***Appellant Claims***

Appellants claim a method as described above in the instant office action.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action. The teachings of Warren were set forth on pages 11-12 of the office action mailed on April 6, 2006 and are restated below in the instant office action.

Warren et al. teach that inhalation of 30 puffs of adrenaline (3 mg) from a pressurized aerosol resulted in peak blood plasma levels of adrenaline ($C_{max}$) of 4.22 ± 1.93 nM after 1 minute ($T_{max}$) of administration. They compared these results to adrenaline administered by a subcutaneous injection, which resulted in peak blood plasma levels of adrenaline ($C_{max}$) of 2.43 ± 0.47 nM after 10 minutes ($T_{max}$) of administration. The blood plasma levels of adrenaline were used as a measure of the systemic absorption of adrenaline (abstract, Figures 1 and 3 on pages 674 and 675, respectively).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Tarara lacks the express teaching of Cmax and Tmax of different administration routes, specifically inhalation administration vs. non-intravenous injection.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

A person of ordinary skill in the art at the time of the instant invention would have been able to obtain information on Warren et al.'s studies showing that the administration of inhaled adrenaline would lead to a shorter time for adrenaline blood plasma levels to reach a maximum concentration as a predictor of what one would expect upon inhalation administration of Tarara's pharmaceutical formulations. A skilled artisan would have known that drug blood plasma levels are a measure of the systemic absorption of a pharmaceutical agent and that said agent would therefore be acting systemically. Based on Warren's data, a person of ordinary skill in the art at the time of the instant invention would have been motivated to administer epinephrine to a patient and would have had a reasonable expectation that said drug administered by inhalation would result in maximal adrenaline blood serum levels in a shorter period of time when compared to non-intravenous injection routes of administration. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(E) Claims 172-173 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 2003/0215512) in view of Tarara et al. (US 2005/0074498) and Slutsky (U.S. Patent No. 6,102,036) as applied to claims 140-143, 146-150, 159, 160, and 162 above, in further view of the *Drug Information Handbook* (1993) ("DIH).

***Appellant Claims***

Appellants claim a method as described above in the instant office action.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Tarara were set forth on pages 3-5 of the office action mailed on April 6, 2006 and have been restated above in the instant office action. The teachings of Slutsky were set forth in the office action mailed on August 7, 2007 and have been restated above in the instant office action. The teachings of the DIH were set forth on page 12 of the office action mailed on April 6, 2006 and are restated below in the instant office action.

The use of epinephrine bitartrate would have been readily apparent to a skilled artisan, because it is one of the most common salts of epinephrine employed in pharmaceutical formulations (*Drug Information Handbook*, Lexi-Comp, Inc.: Cleveland, OH, 1993, pp 322-325).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Tarara lacks the express teaching of the teaching of a composition comprising epinephrine bitartrate.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art to combine the teachings of Tarara/Foster with the DIH, because the DIH is a standard reference used in the pharmaceutical art and the other two prior art references teach pharmaceutical compositions comprising epinephrine. A skilled artisan would have been motivated to combine the teachings of the DIH with those of Tarara and Foster, because epinephrine is a known active agent and epinephrine bitartrate is a common salt of said active used in commercially available pharmaceutical formulations. A person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art references, because Tarara, Foster, and the DIH teach compositions wherein the active is epinephrine, and the bitartrate salt of adrenaline is commonly used in pharmaceutical formulations. Regarding the amount of active agent, Foster teaches an overlapping range for the amount (i.e. about 0.05% to about 99.0% by w/w). In addition, it would have been readily apparent to a skilled artisan per the teachings of Foster that the remainder of the composition would comprise glass-forming excipient (i.e. sodium tartrate) and other additives (e.g. leucine). The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of Appellants' invention. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to

one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

**(10) Response to Argument**

(A) Response to Appellants' traversal of the rejection of claims 140-143, 153, and 156-160 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036).

Appellants traverse the instant rejection by (1) attacking Tarara's teachings in Example XX-XXI and wholly dismissing relevant teachings elsewhere in Tarara as being unreliable, due to mathematical errors in Examples XX-XXI; (2) pointing out that Tarara does not teach actuation of the delivered dose in a single-breath activated step; (3) allegedly there is no reason to select epinephrine (i.e. adrenaline) from the drugs taught as being suitable by Tarara; (4) Slutsky's single-breath actuated inhalers are allegedly less suitable for the delivery of epinephrine to a patient in need of epinephrine who may have difficulty breathing; (5) allegedly there is no motivation to combine the references, because Appellants' claims are allegedly limited to the delivery of epinephrine to a person having difficulty breathing; (6) allegedly the Examiner is missing the point that a skilled person concerned with efficiently delivering epinephrine via inhalation is not concerned with the treatment of glaucoma, but rather is concerned with the treatment of someone as defined in the background section of Appellants' specification; (7) Slutsky is silent as to a teaching of FPF; (8) allegedly Tarara does not disclose tap density; (9) allegedly there is no teaching in Tarara to suggest an amount of epinephrine ranging from about 1 to about 45% w/w (claim 142) or in amount of from about 1 to about 30%

w/w (claim 143); (10) allegedly there is no teaching or suggestion in Tarara for active agent (i.e. epinephrine) amounts of about 250 micrograms to about 5 mgs as recited in claim 153; and (11) allegedly there is no teaching or suggestion of a powder that is designed to deliver epinephrine (i.e. adrenaline) to the upper airways (claim 158), alveoli (claim 157), or both (claim 156) to afford system (claim 159) or local (claim 160) activity.

Regarding arguments (2) and (7), in response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding arguments (1) and (8)-(11), Appellants observation of mathematical errors in Tarara's Examples XX-XXI, contrary to Appellants' opinion, does not render the teachings of Tarara unreliable. It is clear that Tarara's invented inhalable powder compositions have a tap density meeting the recited limitation of a tap density of less than 0.4 g/cm$^3$ (e.g. Examples X-XII [[0276]-[0290]], wherein all the exemplified powders have tap densities of less than 0.1 g/cm$^3$). Clearly the explicit disclosure of powders having a tap density of less than 0.1 g/cm$^3$ meets the limitations of Appellants' claims. It appears that Appellants' focus on the mathematical errors in Tarara's Examples XX-XXI led them to overlook the cited teachings of Tarara regarding tap density.

Tarara clearly teaches that the powders may have a fine particle fraction of approximately 20% or more, such as about 30%, 40%, 50%, 60%, 70%, or 80% by weight [0127]. Tarara clearly identifies epinephrine (i.e. adrenaline) as being a suitable active agent in [0070]. Tarara

clearly teaches that the teachings provide for highly flowable, dry powders that can be efficiently aerosolized, uniformly delivered, and penetrate deeply in the lung and nasal passages [0050]. Tarara clearly teaches that the mean aerodynamic particle size of the invented powders is less than about 5 microns, particularly preferably less than about 2 microns [0126]. Tarara clearly identifies that the range of dry powder than can be filled into a unit dose container is in the range of 5-15 mg, which corresponds to a drug loading in the range of 25-500 micrograms per dose (actuation) [0132] (this meets the limitations of claim 153. The range for the drug dose overlaps with the range recited in Appellant's claims. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Thus, Appellants dismissal of the teachings of Tarara not contained in Examples XX-XXI is unreasonable and unpersuasive and the prior arts' teachings fairly suggest the claimed method.

Regarding (9) and the amount of active agent recited in Appellants' claims 142-143, it is noted that Appellants' specification does not define the term "about" and that both endpoints of the recited ranges are described as "about" a particular value. Furthermore, Tarara explicitly teaches in paragraph [0068] that in some embodiments Tarara's invented powder compositions may comprise 10%, 15%, 20%, 25%, 30% or even 40% active or bioactive agent or alternatively greater than about 50%, 60%, 70%, 75%, 80%, or even 90% active or bioactive agent. Clearly amounts of active ranging from 10%-40% meets the recited amount of epinephrine recited in Appellants' claims 142-143, because about 30% w/w and about 45% w/w both read on an amount of 40% w/w.

Regarding (11), the teachings of Tarara reasonably suggest powder formulations comprising epinephrine and characterized by the same and/or overlapping physical parameters (i.e. average particle size, tap density, and FPF). As a consequence, it is only logical that the inhalation administration of these powder formulations will necessarily result in delivery to approximately the same locations within the respiratory tract and have the same or similar systemic and/or local effects. This is further evidenced, by the fact that dependent claims 156-160 all depend directly from independent claim 140 and do not further limit the physical parameters of the administered powders. Thus, claims 156-160 merely recite the desired result of administration of the powder recited in parent claim 140 and do not impart any new active method steps.

Regarding (3), an ordinary skilled artisan would select adrenaline (i.e. epinephrine) as the active agent, because it is taught by Tarara as being suitable. This teaching is ample motivation to select adrenaline (i.e. epinephrine) as the active, in addition to the fact that Tarara exemplifies compositions comprising an alternative bronchodilator (e.g. albuterol) (e.g. Example XX: [[0276]-[0280]). Thus, the ordinary skilled artisan would have a reasonable expectation of successfully utilizing adrenaline (i.e. epinephrine) as the active agent, because it is explicitly taught by Tarara as being suitable.

Regarding (4)-(6), in response to appellant's argument that the references fail to show certain features of appellant's invention, it is noted that the features upon which Appellant relies (i.e., (i) highly efficient method of delivering epinephrine, (ii) a method of administration that excludes people suffering from glaucoma, (iii) a method of administration limited to people in need of epinephrine in a crisis or emergency situation) are not recited in the rejected claim(s).

Appellants' reliance on what is described in their background section supports the position that Appellants are relying on limitations not found in their claims to argue the unobviousness of the claimed method. Furthermore, regarding Appellants' arguments in reference to the treatment of glaucoma, Appellants have provided no evidence that the inhalation administration of adrenaline (i.e. epinephrine) could not affect the treatment of glaucoma. As currently written, Appellants claims are not limited to the delivery of epinephrine to a patient population that excludes patients suffering from glaucoma. Appellants' specification does not define a "patient in need of epinephrine" as a patient in need of rescue therapy or suffering from anaphylaxis, etc. Thus, Appellants' arguments are unpersuasive and the claimed method can be used in the treatment of glaucoma. Specifically concerning' argument (5), even if one were to construe Appellants' claims as being limited to the delivery of epinephrine to a person having trouble breathing, Appellants' claims do not recite any particular flow rate or resistance as a characteristic of a dry powder inhaler used to administer the recited particles. Appellants have provided no evidence that Slutsky's single breath-actuated inhaler could not deliver Tarara's invented powder compositions to a person having trouble breathing. Attorney argument in the absence of objective evidence is unpersuasive. The arguments are unpersuasive. The rejection is maintained.

(B) Response to Appellants' traversal of the rejection of claims 161-162 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above, and

further in view of Physicians' Desk Reference (PDR, page 1236) (IDS reference, already of record).

Appellants traverse the instant rejection by (1) reiterating the traversal arguments presented to traverse rejection (A) above and (2) arguing that although the PDR teaches that epinephrine (i.e. adrenaline) is known to treat the diseases/conditions recited in claims 161-162 it would be unobvious to treat these diseases/conditions by inhalation administration of epinephrine. The Examiner respectfully disagrees. Regarding (1), the Office's rebuttal of these arguments is herein incorporated by reference. Regarding (2), Tarara teaches highly flowable inhalable powder formulations that are characterized by being able to be aerosolized with high efficiency and uniform dispersion; explicitly identifies epinephrine (i.e. adrenaline) as a suitable active agent for incorporation into the invented powders; and it is well-known that epinephrine is suitable for the treatment of the conditions recited in claims 161-162, as admitted by Appellants. It is thus prima facie obvious to administer an inhalable powder comprising epinephrine (i.e. adrenaline) to treat diseases/conditions for which epinephrine is indicated as being suitable. The rejection is maintained.

(C) Response to Appellants' traversal of the rejection of claims 140-143, 146-150, 159, 160, and 162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 2003/0215512) in view of Tarara et al. (US 2005/0074498) and Slutsky (U.S. Patent No. 6,102,036).

Appellants traverse the instant rejection by arguing that (1) Tarara and Foster cannot be combined, because Tarara teaches porous particles, Foster teaches solid particles, and thus, the

particles of each reference individually is exclusive of the other; (2) the density of Foster's particles necessarily must be greater than that of Tarara's particles and Appellants speculate that Foster's particles must have a density of about 1 g/cm$^3$; (3) the addition of phospholipid as taught by Tarara to Foster's particles would necessarily reduce the glassy nature of Foster's particles; (4) Foster does not teach the FPF limitation; (5) Slutsky's teachings do not "bridge the gap" of the recitation of a single breath-actuated administration, because Slutsky is concerned with the administration of a "very high dose" of nicotine and states that if the dose is sufficiently large it may not be possible to inhale the dose without discomfort; (6) Tarara's Examples XX-XI allegedly render the teaching of Tarara null and void (i.e. no prior art apparently exists that teaches powders similar to those recited in Appellants' claims); (7) Appellants claims allegedly exclude any additional method steps aside from the single breath-actuation; (8) Foster does not teach or suggest an amount of epinephrine ranging from about 1 to about 45% w/w (claim 142) or in amount of from about 1 to about 30% w/w (claim 143); and (9) Foster allegedly teaches away from (i) inhalable particles being amorphous (claim 146), (ii) epinephrine being amorphous (claim 147), (iii) epinephrine being crystalline (claim 148), (iv) excipient being amorphous (claim 149), and (v) excipient being crystalline (claim 150));

Regarding (1)-(3), Appellants' arguments are merely hypotheses, conjectures at best, concerning what they would like to believe would happen upon combination of the teachings of Tarara and Foster. Appellants have provided no objective evidence demonstrating that what they have speculated to necessarily result from the combination of the teachings of Tarara and Foster does actually occur. Attorney argument in the absence of objective evidence is unpersuasive.

Regarding (4), in response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, concerning Appellants' allegation that the data in Foster's table in paragraph [0232] does not correspond to the claimed FPF is incorrect. The claimed FPF is defined as the percentage of particles with a size of less than 5.6 microns and is required to be at least about 45%. In Foster's Table, more than 45 % of Foster's delivered dose consists of particles with a particle size of less than 5 microns, thus meeting Appellants' claimed FPF limitation. In addition as has been stated above, Tarara's teachings include teachings of FPF having values in excess of 45%,

Regarding (5) and (7), Appellants have provided no objective evidence that Slutsky's device is incapable of delivering the dose amounts recited in Appellants' claims. Furthermore, Appellants' claims only describe the administration as requiring a single breath-actuated step. Appellants' claims do not prohibit any method steps occurring prior to the step of administration, as evidenced by Appellants use of "comprising" language to describe the steps of the claimed method. Appellants' argument is unpersuasive.

Regarding (6), this argument has been addressed above in response to the traversal of rejection (A). The Office's rebuttal is herein incorporated by reference. Appellants' argument is unpersuasive.

Regarding (8), in response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA

1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, both Tarara and Foster teach amounts of active agent that overlaps with the amounts recited in Appellants' claims. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Thus, Appellants' argument is unpersuasive.

Regarding (9), Foster teaches that the glass former (i.e. an amorphous excipient) may be used in combination with additives that may by crystalline or amorphous [0064]. Foster also teaches that the drug may be either crystalline or amorphous in form [0055]. Thus, none of these teachings teach away from claims 146-150, because these teachings do not discredit, discourage, or dissuade the ordinary skilled artisan from obtaining amorphous particles, using amorphous and/or crystalline epinephrine, or from using amorphous and/or crystalline excipients. Appellants' claims do not prohibit the compositions from containing both amorphous and crystalline components, nor do Foster's teachings suggest one can only obtain particles comprising solely amorphous or crystalline components. Appellants' argument is unpersuasive. The rejection is maintained.

(D) Response to Appellants' traversal of the rejection of claims 163-170 under 35 U.S.C. 103(a) as being unpatentable over Tarara et al. (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above, and further in view of Warren et al. (*Clin. Pharmacol. Ther.*, 1986, *40(6)*, 673-678) (already of record).

Appellants traverse the instant rejection by arguing that (1) Warren does not suggest or disclose that it would be obvious to administer epinephrine by a breath actuated dry powder

inhaler; (2) Warren does not cure the alleged deficiencies of Tarara and Slutsky concerning the highly efficient delivery of epinephrine in a single breath-actuated adminstration from a dry powder inhaler; (3) the relevance of Warren's teachings concerning claims 163-166 is unclear; (4) although Warren shows that the Tmax for inhalation was shorter that that for injection, because the total doses were different Appellants urge that the limitations in claims 167-169 have not been addressed; and (5) Warren lacks the comparison of Cmax by injection to an aqueous aerosol.

The Examiner respectfully disagrees. Regarding (1), in response to Appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Moreover, the combined teaches of Tarara and Slutsky suggest the inhalation administration of powders characterized by the properties recited in Appellants' claim 140 and comprising epinephrine.

Argument (2) has been addressed above in the previous paragraph. Appellants' argument is unpersuasive.

Regarding (3)-(5), Warren's teachings establish that it was known that the inhalation administration of epinephrine yields a higher Cmax and a shorter Tmax when compared to subcutaneous injection. Thus, Warren's teachings provide a proof of concept and support the notion that administration of Tarara's compositions comprising epinephrine as the active agent using Slutsky's single breath-actuated inhaler would necessarily yield the same or substantially similar pharmacokinetic results as are articulated in Appellants' claims. Furthermore,

concerning (5), in response to Appellant's argument that the references fail to show certain features of Appellant's invention, it is noted that the features upon which Appellant relies (i.e., aqueous aerosol) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Appellants' claim 170 recites that the Cmax comparison is made between the Cmax resulting from administration of Appellants' recited powder formulation versus the Cmax resulting from the administration of a liquid-based aerosol. Appellants' claim 170 does not require the comparison to be between the recited powder composition and an aqueous-based aerosol. Nonetheless, because the teachings of Tarara fairly suggest a powder composition comprising epinephrine and having the required properties of claim 140 it follows that the inhalation administration of Tarara's suggested composition would necessarily exhibit the same or substantially similar Cmax properties when compared to the Cmax resulting from the administration of epinephrine using a liquid-based (e.g. aqueous) aerosol. Appellants' aforementioned arguments are unpersuasive. The rejection is maintained.

(E) Response to Appellants' traversal of the rejection of claims 172-173 under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 2003/0215512) in view of Tarara et al. (US 2005/0074498) and Slutsky (U.S. Patent No. 6,102,036) as applied to claims 140-143, 146-150, 159, 160, and 162 above, in further view of the *Drug Information Handbook* (1993) ("DIH).

Appellants traverse the instant rejection by arguing that (1) despite the fact that both Foster and Tarara identify epinephrine (i.e. adrenaline) as being a suitable active agent for incorporation in their respective formulations there is no reasonable expectation that an ordinary skilled artisan could successfully mix epinephrine with excipients; (2) allegedly there is no suggestion or motivation to select the particular components in Appellants claimed composition (claim 172) or in the composition administered in the claimed method (claim 173); (3) Foster appears to teach a preference for proteins as the active agent and does not identify specific salts of adrenaline that may be used; (4) the amounts of active agent taught by Foster are allegedly so broad that these ranges are essentially meaningless according to Appellants; (5) allegedly the list of glass formers taught by Foster is so numerous that an ordinary skilled artisan would not select sodium tartrate; (6) Appellants' claims require "large amounts" of leucine and leucine is not taught by Foster as being a preferred excipient; (7) Appellants have allegedly shown the criticality of "high amounts" of leucine in the untimely filed declaration with Appellants' appeal brief and also submitted in copending application 10/392,333; (8) Slutsky's inhalers are allegedly unsuitable for the administration of epinephrine to patients in need of epinephrine; (9) Appellants' arguments imply that an ordinary skilled artisan would consider it highly unexpected and surprising that one could mix components well-known in the art, such as leucine, epinephrine bitartrate, and sodium tartrate, in a single formulation; (10) Appellants' compositions allegedly exhibit improved stability and bronchoprotection as evidenced by Appellants' untimely filed declaration.

The Examiner respectfully disagrees with Appellants' arguments.

Regarding (7) and (10), Appellants' declaration data has not been considered because it was not timely filed before the mailing of a final office action and Appellants have not provided good and sufficient reasons as to why they were unable to provide the declaration data prior to the mailing of the final office action on December 10, 2008. See MPEP § 41.33(d)(1) and 37 C.F.R. 1.116(c),(e). Declarations/affidavits submitted after final rejection are subject to the same treatment as amendments after final (MPEP § 710.02(e)(II) and 37 C.F.R. 1.116(c)). It is noted that the instant application does not derive from copending application 10/392,333 nor does the instant application incorporate by reference copending application 10/392,333. Therefore, it is proper for the Examiner to require that extrinsic evidence relied upon by Appellants to allegedly show non-obviousness, which is not contained in the instant application, is provided in a declaration/affidavit. It appears that Appellants filed the declaration submitted with this brief on October 22, 2008 in copending 10/392,333 as well. As a consequence it would not have been an undue burden for Appellants to have timely filed the same declaration before final rejection, and Appellants failure to do so is evidence of the paucity of good and sufficient reasons for its untimely submission. Thus, Appellants' failure to submit the declaration/affidavit before final rejection and failure to provide good and sufficient reasons why the declaration/affidavit was not submitted earlier renders the non-entry of the declaration/affidavit appropriate. The declaration/affidavit has not been considered.

Regarding (1)-(3) and (9), there is no evidence of record that would lead the ordinary skilled artisan to suspect that the combination of epinephrine bitartrate, leucine, and sodium tartrate could not be achieved, such as due to an expectation of some kind of chemical incompatibility of these components when mixed. Appellants' arguments are based on the

speculative assertion that the ordinary skilled artisan necessarily assumes that combination of a well-known active agent with well-known excipients/additives would routinely be untenable and that it would be surprising that one could mix well-known components generally known to be suitable for their stated purposes. If Appellants speculative assertion were correct, then every claimed composition would necessarily require an enablement rejection, because there would be no reasonable expectation, without posing an undue burden, that such a composition could be made. Such is not the state of the art and these speculative arguments absent evidence showing that the ordinary skilled artisan would generally perceive or expect that the claimed composition comprising well-known components would suffer from some kind of incompatibility is unpersuasive.

Regarding (2), the DIH clearly establishes that epinephrine bitartrate is a conventional salt of epinephrine indicated for the treatment of various conditions. Selection of a conventionally used pharmaceutically acceptable epinephrine salt would have been prima facie obvious because it is known to be safe and is readily available. Appellants' formulations comprise epinephrine in the form of a conventionally administered epinephrine salt (epinephrine bitartrate).

Regarding (4), the disclosure of a broad range of active agent in Foster's compositions is an invitation to an ordinary skilled artisan to optimize the amount of a particular active agent to find the optimal amount of said active suitable for the artisan's intended use of said composition. Upon determination of the optimum amount of epinephrine in a particulate formulation it would have been well within the skill of the ordinary artisan to vary the amount of the other conventional additives needed to obtain a composition exhibiting desirable properties. It is also

noted that regarding amounts of active agent that Appellants' specification does not define the meaning of the term about. As a result, even an amount of active agent of 5% w/w would reasonably read on about 11 % w/w active agent. It is also noted that Tarara teaches several embodiments with smaller amounts of active agent (e.g. 10%, 15%, 20%, or 25% w/w), thus the combined prior art does suggest amounts of active agent close to the amount recited in Appellants' claims.

Regarding (5), the selection of sodium tartrate, sodium tartrate is explicitly identified as one of eight preferred glass forming excipients [0072]. Clearly the selection of one glass former from a short list of eight species is not analogous to picking a needle from a hay stack as applied by Appellants.

Regarding (6) a preference is not a teaching away, because it does not discourage, discredit, or dissuade the ordinary skilled artisan from using leucine as one of the excipients in the formulation resulting from the teachings of Foster and Tarara.

Regarding (8), the alleged unsuitability of Slutsky's inhalers has been addressed above and is herein incorporated by reference. Appellants' arguments are unpersuasive. The instant rejection is maintained.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616

Conferees:

/James H. Alstrum-Acevedo/
Patent Examiner, Art Unit 1616
Technology Center 1600

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617